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LITERATURE IN BRIEF

HIV/AIDS Reviews

Lallemant M, Jourdain G, LeCoeur S, Mary JY, Ngo-Giang-Huong N, Koetsawang S, Kanshana S, McIntosh K, Thaineua V; for the Perinatal HIV Prevention Trial (Thailand) Investigators. Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *N Engl J Med*. 2004;351:217–228.

SUMMARY

The efficacy of zidovudine in the prevention of HIV transmission from mother to child was established in 1994. Without treatment, 15–40% of babies born to HIV-positive mothers are infected perinatally. Administration of zidovudine in the last trimester of pregnancy for 6 weeks and intravenously during labor, combined with prophylaxis of the baby with zidovudine for the first 6 weeks of life, reduces the development of HIV infection to 8.3%. Recently published data from Uganda showed that administration of nevirapine as a single dose to the mother at the time of labor and to the baby after birth could significantly lower the risk of transmission even in breastfed infants.

This study is a multicenter, phase 3, double-blind, randomized, placebo-controlled trial that evaluates the efficacy of the addition of nevirapine to women in the third trimester of pregnancy who are already receiving zidovudine. The study was conducted in Thailand where there is a government-funded program of voluntary counseling and testing of pregnant women. All women received 300 mg of zidovudine twice daily, starting at 28 weeks of gestation or as soon as possible thereafter. This regimen was changed to 300 mg every 3 hours from the onset of labor until delivery. Infants received zidovudine, 2 mg/kg of body weight, in an oral suspension every 6 hours for 1 week. If the mother had received less than 4 weeks of zidovudine, the baby was treated for 6 weeks. Three treatment groups were evaluated. In the nevirapine–nevirapine group, the mother received a single 200-mg dose at the onset of labor and the baby received oral suspension (6 mg fixed dose) between 48 and 72 hours after birth. In the placebo–placebo group, mother and child received placebo at the same time as the first group. In the nevirapine–placebo group, the mother received additional nevirapine, whereas the child received a placebo.

Infants were considered infected if two HIV polymerase chain reaction tests on blood were positive after 1 month of age. These tests were done at 6 weeks and 4 and 6 months after birth. Two interim analyses were carried out. At the first interim analysis, the placebo–placebo arm was discontinued because the transmission rate in the nevirapine–nevirapine group was 1.1% compared with 6.3% in the placebo arm. The final analysis showed that the transmission rate in the nevirapine–nevirapine group (1.9%) was not statistically significantly different from that in the nevirapine–placebo group (2.8%). Interestingly, women with baseline viral loads less than 25,000 copies/mL had a transmission rate of only 2% in the placebo–placebo group, only marginally greater than that in the nevirapine groups.

COMMENTARY

This study highlights the very important concern of mother-to-child transmission in the pandemic of HIV. The treatment of HIV infection in children in resource-poor settings is particularly daunting. The administration of combination antiretroviral therapy, Cesarean sections, and formula feeding, unavailable in some resource-poor countries, have dramatically reduced the transmission of HIV from mother to child from 25 to 1–2% in industrialized countries. Further reduction of transmission with the addition of a single dose of nevirapine to standard zidovudine to the mother at the time of labor and delivery is a simple intervention with a potentially large reward. However, as has been previously shown, there is a concern for the development of resistance to non-nucleoside reverse transcriptase inhibitors after the administration of a single dose of nevirapine, which might jeopardize future antiretroviral treatment for the mother and child. The key to avoiding this development is maintaining low viral loads during pregnancy. Low viral loads during pregnancy are of great value in reducing the rate of transmission and make a strong case for the treatment of these high-risk women.

Lucas GM, Weidle PJ, Hader S, Moore RD. Directly administered antiretroviral therapy in an urban methadone maintenance clinic: a nonrandomized comparative study. *Clin Infect Dis*. 2004;38(suppl 5):S409–S413.

SUMMARY

Adherence to medications is a major concern in all conditions where prolonged treatment is required. This study reports on the interim results of an ongoing directly administered antiretroviral therapy (DAART) protocol at a university-associated methadone clinic. Patients who were starting antiretroviral therapy or changing antiretroviral therapy for treatment failure were recruited from a methadone clinic where they had received therapy for more than 30 days. Patients received one dose of directly administered therapy on the days that they were in the clinic. Evening doses and doses on methadone take-home days were provided in prepackaged units. DAART staff members provided education about HIV, inquired about treatment-related difficulties, facilitated communication with primary care providers, and helped participants to gain access to medical and social services. Comparison groups drawn from the HIV clinic of the same institution consisted of people who received standard care and people who were part of an adherence support group. Comparison groups included individuals with a history of injection drug use, and where possible, comparison patients receiving methadone were selected.

Among the three groups, the proportion of patients who achieved suppression of HIV1-RNA levels to less than 400 or less than 50 copies/mL by month 6 of therapy was compared by an intention-to-treat, missing-equals-failure rule. Most DAART participants were from a special clinic for HIV-infected uninsured women. Among DAART participants, 79% compared with 54% in the standard treatment group ($P = .035$) and 48% in the adherence support group ($P = .008$) achieved HIV-RNA less than 400 copies/mL by 6 months. In the DAART group, 58% compared with 22% in the standard care group ($P = .002$) and 23% in the adherence support group ($P = .003$) achieved levels of HIV-RNA less than 50 copies/mL. RNA levels were not significantly different between standard care and adherence support groups ($P = .37$). Median increase in CD4 counts was 72 cells/mm^3 in the DAART group, 31 cells/mm^3 in the standard care group, and 52 cells/mm^3 in the adherence support groups.

COMMENTARY

Directly observed therapy is an attempt to ensure patient adherence to medications. It has been used successfully in tuberculosis control programs as a means of treatment and prevention of spread. In the case of HIV, there are some inherent differences—treatment often needs to be twice a day, no once-weekly treatment options are available, constant monitoring is needed, and change in therapy may frequently be required. All these factors make a directly observed therapy-like approach difficult. This study proposes a modified use of such a treatment strategy in a particular setting, that of methadone clinics. HIV is highly prevalent in this population, and problems of adherence are common. Nearly 80% of the population enrolled, compared to 50% in comparison groups, experienced viral suppression. Of note is the unique opportunity this presents, of increasing the interaction between health care personnel and patients, allowing a more integrated and continual dialogue, which may not occur as effectively in a busy HIV clinic. This may provide yet another link in the chain between the health care providers and patients.

The study, however, has certain limitations. It is nonrandomized, and selection and other biases may affect comparisons. Also, nearly 40% of the participants dropped out during the first 6–12 months, consisting mostly of the individuals who defaulted from methadone therapy. However, further investigation of this concept may lead to the development of a more integrated social and medical system and eventually lead to greater compliance and less strain on the medical system posed by opportunistic infections and other complications of HIV.

Smith CJ, Sabin CA, Youle MS, et al. Factors influencing increases in CD4 cell counts of HIV-positive persons receiving long-term highly active antiretroviral therapy. *J Infect Dis*. 2004;190:1860–1868.

SUMMARY

The debate on factors contributing to immune reconstitution in HIV-positive individuals has been long-lived. This study examines and reexamines some of the factors that might have an impact on the ultimate immunological outcome. Five hundred and ninety-six HIV-positive combination antiretroviral therapy-naïve individuals were followed for an average of 2.5 years after beginning combination antiretroviral therapy (≥3 antiretrovirals), and factors associated with changes in CD4 cell count at 3 months and after 3 months were evaluated. Most patients were male (74%) and of white ethnicity (63%).

A good response to therapy was observed with only 8–10% discontinuing antiretrovirals between 6 and 36 months. Median increase from baseline CD4 cell count was 114 cells/mm^3, with 84% achieving viral loads less than 400 copies/mL at 6 months. Factors contributing to the increase in CD4 cell counts in the first 3 months were lower pretherapy CD4 and CD8 cell counts, white ethnicity, and higher pretherapy viral load. After the initial 3 months, factors of significance appeared to be lower pretherapy CD4 cell count, a viral load less than 400 copies/mL, and starting highly active antiretroviral treatment after 1997. It was also noted that as the cumulative time spent with a viral load less than 400 copies/mL increased by 10%, there was an additional increase in CD4 cell count of 5.1 cells/mm^3/year.

COMMENTARY

HIV is a chronic debilitating condition, and it would be useful to identify factors that could help predict the response to therapy. Studies done over the years have repeatedly stressed the

significance of factors such as adherence, baseline CD4 cell counts, and viral load. The results of this study agree with those of others that have shown that prolonged viral suppression results in a greater increase in CD4 cell counts in the long term. However, it differs because most other studies have shown that higher and not lower baseline CD4 cell counts are associated with better overall immunological responses. This result may be due to the improved antiretroviral armamentarium that has been developed over the last 15 years. This effect though statistically significant is of small magnitude. Demographic factors in general have not provided much predictability of response. Additionally, factors such as adherence, coinfection with hepatitis C, intravenous drug use, and host and viral genetic factors and the effects of discontinuing all antiretrovirals have not been considered.

Even though good virologic control is of great significance, most of the benefit from immune reconstitution is reflected in improved CD4 cell counts, which is associated with a decrease in the incidence of opportunistic infections. From a clinical perspective, a robust CD4 count increase even in the presence of persistent viremia is not an indication of treatment failure. However, the long-term outcome of an elevated viral load continues to be a subject of concern.

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